ORIGINAL ARTICLE

CONTENTS

Effect of ivabradine on structural and functional changes of myocardium and NT-proBNP levels in patients with stable coronary heart disease after coronary stenting

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ABSTRACT

Aim: To investigate the effect of ivabradine on the hemodynamics and contractility of the myocardium and the features of NT-pro-BNP production in patients with stable ischemic heart disease after endovascular revascularization of the myocardium depending on the number of affected coronary arteries during 12 months of therapy.

Materials and Methods: The object of the study was 120 patients with stable coronary artery disease: angina pectoris of functional class III with heart failure IIA FC III with preserved and moderately reduced ejection fraction of the left ventricle, who underwent coronary artery stenting. The examined patients were randomized according to the number of affected coronary vessels and the method of treatment.

Results: Ivabradine in patients with stable ischemic heart disease after 12 months of therapy had a significant beneficial effect on the structural and functional parameters of the myocardium (contributed to the reverse remodeling of the left ventricle), which did not depend on the number of stented coronary arteries ($p<0.05$). In patients with stented one coronary artery, all structural and functional indicators of the heart after 12 months of treatment reached the values of practically healthy individuals from the control group. The use of ivabradine in patients with stable ischemic heart disease with heart failure with preserved and intermediate ejection fraction of the left ventricle after coronary stenting made it possible to ensure the correction of a number of clinical and pathogenetic links of the disease, which generally contributed to the improvement of metric and volumetric parameters of the heart.

Conclusions: Ivabradine made it possible to significantly increase the effectiveness of standard therapy, which was manifested by a faster recovery of the geometry and contractility of the left ventricle. Therefore, the use of ivabradine along with standard therapy was appropriate for such a contingent of patients. The management of patients with stable coronary heart disease should combine adequate (surgical and pharmacological) treatment of the underlying disease, further individual medication correction of symptoms and circulatory disorders inherent in coronary heart disease and heart failure.

KEY WORDS: stable ischemic heart disease, coronary arteries, stenting, heart failure, ivabradine

Wiad Lek. 2024;77(4):800-810. doi: 10.36740/WLek202404128 DOI

INTRODUCTION

Throughout the world, cardiovascular diseases (CVD) are the main cause of mortality and disability of the population. Among cardiac pathologies, ischemic heart disease (IHD) occupies a leading position [1]. IHD is projected to cause 23.4 million deaths by 2030, compared to 18 million in 2017 [2]. Ischemic heart disease is a disease caused by atherosclerosis of the coronary arteries (CA) with significant stenosis (≥ 50%). Coronary obstruction, ischemia, hypoxia, and necrosis of the myocardium, which profoundly affects both the structure and functions of the heart, thereby increasing the risk of acute myocardial infarction and heart failure (HF) are at the heart of the pathogenesis of IHD. [3, 4].

HF syndrome is a global problem of WHO, progressing in both developed and developing countries [5]. Heart failure is the most common cardiovascular cause of hospitalization, especially among patients over 60 years of age [6].

In the treatment of patients with coronary heart disease, it is important to improve the quality of life, which for the patient consists in the absence of angina attacks, improvement of tolerance to physical exertion, control of heart rhythm disorders. Today, the issue of controlling the symptoms of angina pectoris remains problematic, especially in conditions of chronic stress. Both 1st and 2nd line drugs are used to reduce the severity of the pain syndrome, in accordance with the recommendations of the European Society of Cardiology, [7].

An alternative method of treating such patients today is surgical revascularization of the myocardium, that is, the removal of stenoses of the coronary vessels in order to fully restore blood flow in the myocardium, which will eliminate polypharmacy, because old age and polyphar-

macy have been recognized as significant predictors of the problem of drug therapy [8]. Currently, there are three main options for coronary revascularization: coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), and stenting of coronary artery (CA). Patients with multiple coronary artery disease appear to have better outcomes with CABG. Minimally invasive bypass surgery is an evolving technique and its use is limited, and its advantages over traditional CABG have not yet been proven. Currently, CA stenting plays a significant role in percutaneous revascularization and is performed in more than two-thirds of all interventional procedures and improves long-term results in the treatment of CAD [9]. The choice of treatment depends on many factors, including the patient's age, comorbidities, the number and location of the affected CAs, and the severity of the cardiovascular pathology.

The ESC/EACTS Guidelines on myocardial revascularization (2018) state that only the infarct-related artery should be revascularized [10]. However, there are many randomized controlled trials that suggest a strategy of total revascularization, either during primary PTCA may be beneficial and safe in a selected population of patients with CHD. [11–14].

CHD treatment options and regimens have changed over the past few years and are likely to continue to evolve. Drug-eluting stents (DES) are an available treatment. They reduce the frequency of restenosis and, therefore, the frequency of repeated revascularizations. Solirimus-eluting stents are a real device with a very good safety profile and long-term clinical efficacy [15]. They may also be an important treatment option for people with diabetes and multivessel disease who have had the best results with CABG [9].

The recovery of symptoms of heart ischemia with the development and progression of chronic heart failure (CHF) in this category of patients is associated with a sufficiently large number of unfavorable prognostic factors, the most important of which are the severity of the patient's condition before percutaneous coronary intervention (PCI), the development of restenosis and stent thrombosis after stenting, heart rhythm disturbances and progression of dyslipoproteinemia as the main factor of coronary atherosclerosis [16].

Percutaneous coronary intervention is of crucial importance for the restoration of CA function [17]. Cardiac rehabilitation is a well-recommended and scientifically proven approach that includes patient education, behavior modification techniques, and exercise to significantly improve secondary prevention outcomes in patients diagnosed with CVD [18]. The safety of early complete recovery after PCI has been established [19-21]. So, from the above, it becomes quite clear the importance of one of the problems in modern cardiology - treatment and rehabilitation of patients who have undergone endovascular interventions for CA.

The importance of quantitative determination of the levels of natriuretic peptides (NUP) in plasma has attracted great attention of heart pathology researchers in recent years. These markers are believed to be released from the myocardium in response to wall stretch, and their levels correlate with the severity of heart failure. According to the NICE recommendations, even a slight increase in the number of NUP indicates the beginning of the development of HF [22]. Therefore, one of them - N-terminal pro-B-type NUP (NT-proBNP) is widely used in diagnosis and monitoring the effectiveness of HF treatment. Moreover, recent studies have shown the potential utility of NT-proBNP for the monitoring of CHF and selection of drug therapy [23].

It was established that NT-pro-BNP is secreted in normal amounts in healthy people mainly by the left ventricle. In patients with left ventricular (LV) dysfunction, the rate of NT-про-BNP secretion increases in proportion to the increase in LV pressure. In view of this relationship, Yasue et al. (1994) suggested the use of an increased level of NT-p-BNP in blood serum as a diagnostic and prognostic marker of cardiac dysfunction in patients with CHF on the background of IHD [24, 25].

Despite medically corrected angina, the myocardium of stented or shunted patients with chronic obstructive pulmonary disease is still remodeled in the course of life, which leads to the development or progression of HF. And that is why it is necessary to pay attention to the early markers of its development - the dynamics of NT-ppoBNP. So, from the above, it becomes quite clear the importance of one of the problems in modern cardiology - treatment and rehabilitation of patients who have undergone endovascular interventions for CA.

Pharmacotherapy of CHD with different drug classes - beta-blockers, calcium channel antagonists and nitrates - plays an important role in reducing heart rate (HR), thereby reducing the risk of tachycardia-related mortality. Although these drug classes have clinical applications in many cardiovascular diseases, they lack selectivity and specificity in reducing heart rate and are often associated with adverse effects [26]. For the treatment of patients with stable coronary heart disease (CHD), especially after undergoing PCI, the proposal to use a medicinal product with a fundamentally new mechanism of action, capable of reducing heart rate in order to increase blood supply to the heart muscle without negatively affecting other organs and systems of the patient, becomes attractive. Ivabradine is the first drug in a new therapeutic class with a long-lasting and persistent effect, which exhibits an antitachycardic

effect on the heart by selective and specific inhibition of If-sodium channels of pacemaker cells of the sinus node, which provides wide opportunities for its use in patients with CVD who need to reduce the heart rate (HR), which is confirmed by randomized controlled trials such as BEAUTIFUL, SHIFT and SIGNIFY [26, 27].

Despite the obtained positive effects of reconstructive and medical therapy of CAD, the effects of basic therapy using β-adrenoblockers (β-AB) and ivabradine on the clinical course of CAD, myocardial viability and coronary reserve for predicting outcomes after endovascular revascularization of the heart in patients remain unclear. who underwent coronary artery stenting, depending on the number of affected vessels in the remote period, which is the relevance of this study.

AIM

The purpose of the study was to investigate the effect of ivabradine on the hemodynamics and contractility of the myocardium and the features of NT-pro-BNP production in patients with stable ischemic heart disease after endovascular revascularization of the myocardium depending on the number of affected coronary arteries during 12 months of therapy.

MATERIALS AND METHODS

The study included 120 patients with coronary heart disease: angina pectoris, functional class (FC) III. Diffuse cardiosclerosis. HF IIA FC III with preserved and moderately reduced ejection fraction (EF) of the left ventricle (LV) and 15 practically healthy individuals, representative by age and sex. Among the examined, men predominated - 101 people (84.2%). The average age of the patients was 61.4±0.5 years. Our data agree with the data of other studies that male gender and age are important unmodified risk factors for the development of CHD [28]. The normal control group consisted of 15 practically healthy people (3 women and 12 men) with an average age of 60.0±0.8 years.

After analyzing the frequency of risk factors and accompanying pathology, it was established: arterial hypertension (AH) of the II-III stage of the 2nd degree in 51 (88.0%) and 55 (88.7%) patients of the main group (MG) and the group comparison (CG), respectively; compensated type 2 DM occurred exclusively in subgroups of patients with multiple vascular lesions in 10 (17.3%) and 9 (14.5%) of the studied MG and the CG, respectively; excess body weight was diagnosed in 35 (60.3%) and 33 (54.9%) patients of both groups; obesity of the 1st degree in 14 (17.2%) and 15 (19.4%) patients of MG and CG, respectively; dyslipidemia was established in 51 (87.9%) and 49 (79.0%) patients with MG and CG, respectively; commitment to smoking was noted in 43 (74.1%) and 49 (79.0%) patients of MG and CG. The data of other researchers are similar [29, 30, 31].

Diagnosis and treatment were carried out according to the Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care «Stable coronary heart disease» 2021 [32], recommendations of the Heart Failure Association (HFA) ESC 2023 [33].

Depending on the treatment, the patients were divided into 2 groups. The main group (MG) included 58 patients who, together with the basic treatment, took ivabradine at a dose of 12.55±1.94 mg/day. Among the drugs of basic therapy (BT), patients were recommended acetylsalicylic acid in a dose of 75 mg/day, clopidogrel — 75 mg/day, bisoprolol — 2.5 mg/day, ramipril — 8.61±2.85 mg/day or losartan — 84,62±24.02 mg/day, atorvastatin — 36.55±7.62 mg/day. Among MG patients, 15 individuals with single-vessel and 43 with multi-vessel lesions of CA were recorded. The comparison group (CG) included 62 patients who underwent percutaneous coronary intervention percutaneous coronary intervention (PCI) with coronary artery stenting and BT drugs were prescribed - acetylsalicylic acid at a dose of 75 mg/day, clopidogrel — 75 mg/day, bisoprolol — 7.56±2.53 mg/day, ramipril — 5.90±2 .58 mg/day or losartan — 63.33±22.89 mg/day, atorvastatin — 36.77±7.42 mg/day. In 16 patients with AH, a lesion of one CA was established, in 46 – a multivessel coronary lesion. All patients before PCI and 6 and 12 months after coronary stenting (CS) and the proposed medical treatment to assess the activity of the myocardium, intracardiac hemodynamics, and the typical and functional state of the myocardium had their NT-proBNP level determined and echocardiography (EchoCG) performed.

Coronary angiography (CAG) was performed with consent and in the absence of contraindications to all patients. The interventional angiographic system Infinix-sCore+INFX-8000V (InfinixVF-i/SP)/G3, Toshiba (Japan) was used for this study. Access to the spacecraft was carried out through a. radialis; Ultravist 370 mg/ml, Omnipaque 350 mg/ml or Visipaque 320 mg/ml were used to contrast vessels. The SYNTAX revascularization index was taken into account, which determines the severity and degree of initial coronary artery disease and its course after PCI and has prognostic value in further treatment [34, 35].

In order to optimally choose the method of myocardial revascularization, the Syntax Score 1 and Syntax Score 2 indices were calculated. According to the results of those indices, patients were included in the study, in whom, according to the value of these indices, it was necessary

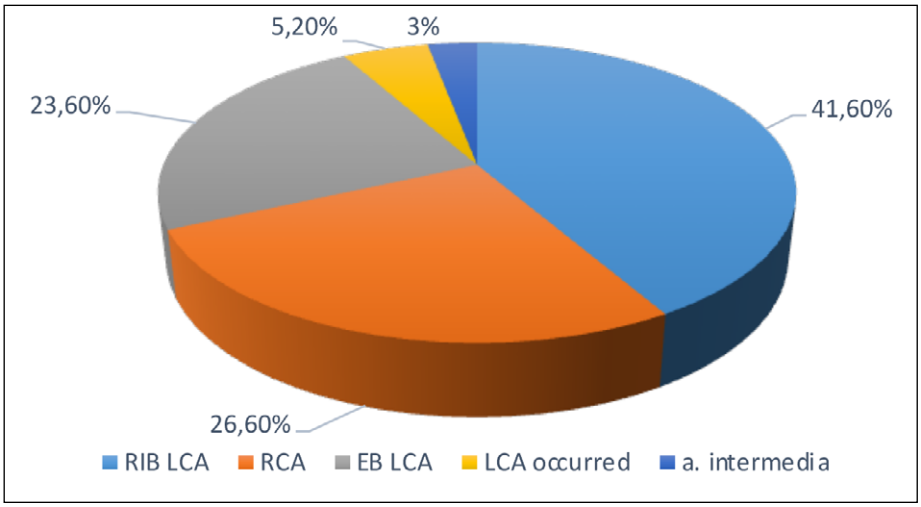

Fig. 1. The structure of coronary artery lesions in patients with coronary heart disease: angina pectoris FC III with HF IIA FC III with preserved LVEF.

to perform PCI by stenting coronary vessels - http://www.syntaxscore. com/calculator/start.htm [36]. Resolute Integrity (Medtronic, USA) zotarolimus-coated stents (DES-type stents) were used for CA dilation in all subjects.

Echocardiography was performed using a Philips device, HD11 XE (Germany), using a 2.5 MHz sensor and using M- and B-scanning modes. End-diastolic (EDD) and end-systolic (ESD) dimensions of the LV, end-diastolic (EDV) and end-systolic (ESV) volumes of the LV and LVEF were determined.

Determination of the level of NT-proBNP in the blood was carried out on the enzyme immunoassay «Stat-Fax 2100» of AWARENESS Technology, Inc. (USA) using «BIOMEDICA MEDIZINPRODUKTE» kits (GmbH&Co Austria), according to the manufacturer's method. Normal limits of NT-proBNP <350 fmol/ml (CH is absent), 250-350 fmol/ml is a gray zone (CH is possible), > 350 fmol/ml (CH is present).

The statistical processing of the obtained results was carried out with the help of the STATISTICA-8 computer program and the package of statistical functions of the program «Microsoft-Excel» on a personal computer, using the variational statistical method of analysis. At the same time, the arithmetic mean M, the mean square deviation δ, the mean error of the mean arithmetic m, the number of the variant (n), the probability of the difference between the two mean arithmetic «p» were calculated; values of $p<0.05$ were considered probable.

RESULTS

According to CAG data, the right type of myocardial blood supply was determined in 108 patients (90.0%), in 10 (8.3%) - left, and in 2 (1.7%) - undetermined. According to the results of the analysis of the Syntax Score I scale, it was established that in 31 patients with single-vessel atherosclerotic lesions of the CA, the number of points was 8.77±1.31, with lesions of two coronary arteries - 13.83±2.07 points, with stenosis of three coronary vessels - 17.92±3.01 points. Damage to the trunk of the left coronary artery (LCA) was not detected in any of the examined, and in 33 (27.5%) people, a stenotic narrowing of the proximal part of the anterior interventricular branch (AIB) of the LCA was established. The results of the analysis of the Syntax Score II scale in 87 (72.5%) cases made it possible to give preference to PCI, and in the rest - did not give preference to PCI over CABG. In this part of patients, the decision to choose a revascularization method was made according to the recommendations of the European Society of Cardiology (ESC), the European Association of Cardiothoracic Surgeons (EACTS) and with the participation of the European Association of Interventional Cardiologists in 2018 [37].

A single-vessel lesion of the CA, confirmed by the CAG method, was found in 31 (25.8%) patients, and a multi-vessel lesion of the CA was found in 89 (74.2%) patients, with two affected vessels in 65 (54.2%), and three affected vessels – in 24 (20.0%) patients.

In general, CA damage in quantitative terms: damage to RIB LCA usually prevailed - in 41.6% of patients, as well as right CA (RCA) - 26.6% and enveloping branch of LCA (EB LCA) - 23.6%, rarely lesions of the diagonal branch (DB) of the LCA occurred in 5.2% and a. intermedia - in 3% of patients (Fig. 1).

All 120 patients were divided depending on the number of affected coronary vessels after CAG. There were 15 (25.9%) cases of patients with a single-vessel lesion in the MG, and 16 (25.8%) cases in the CG. Multivessel lesions of CA were found in 43 (74.1%) cases of MG patients and in 46 (74.2%) patients with AH. Two-vessel lesion of CA was established in 31 (53.4%) patients with MG and in 34 (54.8%) patients with AH, and three-vessel lesion - in 12 (20.7%) and 12 (19.4%) in cases of MG and CG, respectively. The

Table 1. Dynamics of structural and functional changes of the myocardium under the influence of ivabradine in patients with CIHD after CA stenting

Indicator	Healthy (n = 15)	At the moment hospitalization		After treatment			
				Stented one CA		Stented several CA	
		Damage to one CA (n = 15)	Damage to several CAs (n = 43)	6 months (n = 15)	12 months (n = 15)	6 months (n = 43)	12 months (n = 43)
1	2	3	4	5	6	7	8
LA, sm p, Δ%;	3,59±0,02	3,99±0,04 p_{2-3}<0,05	4,31±0,08 p_{2-4}<0,05 p_{3-4}<0,05	3,75±0,06 p_{3-5}<0,05 6,0%	3,61±0,03 p_{3-6}<0,05 p_{5-6}<0,01 9,5%	4,06±0,06 p_{4-7}<0,05 5,8%	3,85±0,06 p_{4-8}<0,05 p_{7-8}<0,05 10,7%
EDD LV, sm p, Δ%;	5,21±0,03	5,79±0,08 p_{2-3}<0,05	6,19±0,09 p_{2-4}<0,05 p_{3-4}<0,05	5,57±0,05 p_{3-5}<0,05 3,9%	5,37±0,05 p_{3-6}<0,05 p_{5-6}<0,01 7,3%	5,97±0,06 p_{4-7}<0,05 3,7%	5,78±0,04 p_{4-8}<0,05 p_{7-8}<0,05 6,6%
ESD LV, sm p, Δ%;	3,80±0,03	4,36±0,06 p_{2-3}<0,05	4,67±0,06 p_{2-4}<0,05 p_{3-4}<0,05	4,11±0,05 p_{3-5}<0,05 5,7%	3,93±0,05 p_{3-6}<0,05 p_{5-6}<0,01 9,9%	4,48±0,06 p_{4-7}<0,05 4,1%	4,34±0,05 p_{4-8}<0,05 p_{7-8}<0,05 8,1%
EDV LV, sm p, Δ%;	130,13±3,85	166,27±5,22 p_{2-3}<0,001	193,02±6,40 p_{2-4}<0,001 p_{3-4}<0,05	151,67±3,42 p_{3-5}<0,05 8,8%	139,00±2,93 p_{3-6}<0,05 p_{5-6}<0,05 16,4%	177,63±4,10 p_{4-7}<0,05 8,0%	165,70±2,76 p_{4-8}<0,05 p_{7-8}<0,05 14,2%
ECV LV, sm p, Δ%;	62,07±2,15	85,93±3,01 p_{2-3}<0,05	100,82±3,30 p_{2-4}<0,05 p_{3-4}<0,05	74,67±2,97 p_{3-5}<0,05 13,1%	67,33±1,95 p_{3-6}<0,05 p_{5-6}<0,05 21,6%	91,23±2,40 p_{4-7}<0,05 9,5%	84,86±2,45 p_{4-8}<0,05 p_{7-8}<0,05 18,1%
PV, ml p, Δ%;	68,07±320	80,53±2,75 p_{2-3}<0,05	92,20±2,01 p_{2-4}<0,05 p_{3-4}<0,05	76,73±2,58 p_{3-5}<0,05 4,7%	71,27±1,49 p_{3-6}<0,05 p_{5-6}<0,05 11,5%	86,35±2,81 p_{4-7}<0,05 6,3%	80,79±2,14 p_{4-8}<0,05 p_{7-8}<0,05 12,4%
EF LV, % Δ%	55,94±0,68	51,07±1,22 p_{2-3}<0,05	48,37±0,69 p_{2-4}<0,05 p_{3-4}<0,05	54,07±0,59 p_{3-5}<0,05 5,5%	55,53±0,59 p_{3-6}<0,05 p_{5-6}<0,05 8,0%	50,97±0,41 p_{4-7}<0,05 5,1%	53,94±0,64 p_{4-8}<0,05 p_{7-8}<0,05 10,3%

Note: The indicators presented in % are in relation to the figures at the time of hospitalization.

clinical effectiveness of the treatment was evaluated and compared before CA stenting, 6 and 12 months after PCI.

The addition of BT ivabradine during 12 months of treatment changed the structural and functional state of the heart in patients with CHD (Table 1): the sizes of the left atrium (LA) and LV and its volumetric parameters - end systolic volume (SVV) - decreased statistically significantly, end diastolic volume (EDV) and PV ($p<0.05$). Ivabradine also optimized the contractile capacity of the LV - the increase in PV was reliably pronounced. It should be noted that during the entire period and at all stages of observation, a significant improvement in the structural and functional parameters of the heart was noted in MG patients, which was significantly different from the similar data of patients with AH (tables 1, 2). In MG patients with stented one coronary artery, all structural and functional indicators of the heart after 12 months of treatment reached the values of practically healthy individuals from the control group.

In MG patients with stented one coronary artery, 6 months after treatment, LVEF increased by 5.5%, and in similar patients, AH increased by 3.5% ($p<0.05$). LV ejection fraction increased by 5.1% in MG patients with stented multiple CAs, and by 2.6% in similar AH patients ($p<0.05$).

On the 12th month of treatment in MG patients who were stented with one and several CAs, the dynamics of LVEF had a positive increase and amounted to 55.53±0.52% and 53.94±0.64%, respectively, which is by 8.0 % and was 10.3% more than at the time of hospitalization ($p<0.05$). At the end of the study, the pumping function of the heart in AH patients with stented single and multiple CAs also tended to increase, but with less pronounced dynamics: LVEF (1 CA) increased by 4.3% and by 3.0% (2 and > CA).

Table 2. Structural and functional changes of the myocardium under the influence of BT drugs in patients with CIHD after stenting of one and several CAs

Indicator	Healthy (n = 15)	At the moment hospitalization		After treatment			
				Stented one CA		Stented several CA	
		Damage to one CA (n = 16)	Damage to several CAs (n = 46)	6 months (n = 16)	12 months (n = 16)	6 months (n = 46)	12 months (n = 46)
1	2	3	4	5	6	7	8
LA, sm p, Δ%;	3,59±0,02	3,91±0,01 p_{2-3}<0,05	4,24±0,05 p_{2-4}<0,05 p_{3-4}<0,05	3,85±0,05 p_{3-5}<0,05 1,5%	3,82±0,04 p_{3-6}<0,05 p_{5-6}>0,05 2,3%	4,15±0,11 p_{4-7}<0,05 2,1%	4,10±0,13 p_{4-8}<0,05 p_{7-8}>0,05 3,3%
EDD LV, sm p, Δ%;	5,21±0,03	5,74±0,08 p_{2-3}<0,05	6,12±0,08 p_{2-4}<0,05 p_{3-4}<0,05	5,65±0,05 p_{3-5}<0,05 1,6%	5,62±0,04 p_{3-6}<0,05 p_{5-6}>0,05 2,1%	6,06±0,08 p_{4-7}<0,05 1,0%	6,03±0,10 p_{4-8}<0,05 p_{7-8}>0,05 1,5%
ESD LV, sm p, Δ%;	3,80±0,03	4,33±0,07 p_{2-3}<0,05	4,62±0,08 p_{2-4}<0,05 p_{3-4}<0,05	4,28±0,04 p_{3-5}<0,05 1,2%	4,26±0,05 p_{3-6}<0,05 p_{5-6}>0,05 1,6%	4,56±0,05 p_{4-7}<0,05 1,3%	4,54±0,08 p_{4-8}<0,05 p_{7-8}>0,05 1,7%
EDV LV, sm p, Δ%;	130,13±3,85	163,38±2,70 p_{2-3}<0,001	187,21±5,53 p_{2-4}<0,001 p_{3-4}<0,05	157,00±3,10 p_{3-5}<0,05 3,9%	155,13±2,42 p_{3-6}<0,05 p_{5-6}>0,05 5,0%	184,26±5,81 p_{4-7}<0,05 1,6%	182,04±7,27 p_{4-8}<0,05 p_{7-8}>0,05 2,8%
ECV LV, sm p, Δ%;	62,07±2,15	84,43±2,89 p_{2-3}<0,05	95,63±2,94 p_{2-4}<0,05 p_{3-4}<0,05	81,50±2,00 p_{3-5}<0,05 3,5%	79,56±3,33 p_{3-6}<0,05 p_{5-6}>0,05 3,5%	95,04±2,47 p_{4-7}<0,05 0,6%	94,30±3,43 p_{4-8}<0,05 p_{7-8}>0,05 1,4%
PV, ml p, Δ%;	68,07±320	78,95±2,50 p_{2-3}<0,05	91,57±4,44 p_{2-4}<0,05 p_{3-4}<0,05	78,31±1,45 p_{3-5}<0,05 0,8%	76,69±3,03 p_{3-6}<0,05 p_{5-6}>0,05 2,9%	89,20±2,98 p_{4-7}<0,05 2,6%	87,74±7,78 p_{4-8}<0,05 p_{7-8}>0,05 4,2%
EF LV, % Δ%	55,94±0,68	51,22±0,74 p_{2-5}<0,05	48,91±0,54 p_{2-6}<0,05 p_{5-6}<0,05	53,06±0,68 p_{3-5}<0,05 3,5%	53,50±0,73 p_{3-6}<0,05 p_{5-6}>0,05 4,3%	50,23±0,28 p_{4-7}<0,05 2,6%	50,45±0,45 p_{4-8}<0,05 p_{7-8}>0,05 3,1%

Ivabradine contributed to the reduction of the volumetric parameters of the heart chambers, in particular the EDV, during the entire observation period, regardless of the number of stented coronary arteries. In patients with stented one coronary artery, after 12 months of follow-up, the value of EDV came as close as possible to the values of practically healthy individuals, that is, it decreased by 16.4%, and in similar patients with AH by 5.0% (p<0.05), with stented several coronary arteries - by 14.2%, in similar patients, BP decreased by only 2.8% (p<0,05).

The LV end-diastolic volume of patients of both groups after stenting of one CA at the 6th month of treatment decreased compared to admission, but with more pronounced changes in MG patients.

Already after 6 months of treatment, Ivabradine significantly improved the size of the LA and LV in patients with CIHD compared to BT. Thus, in patients with stented one coronary artery, after half a year of observation, the diameter of the left atrium decreased by 6.0% versus 1.5% in the LA (p<0.05), the LV EDD decreased by 3.9 versus 1.6% (p<0 .05), LV ESD - by 5.7% versus 1.2%, (p<0.05), LV ESV by 13.1% versus 3.5% (p<0.05), respectively. The decrease in PV by 4.7% versus 0.8% in MG and AH patients, respectively, indicated optimization of the LV contractile capacity by ivabradine and was confirmed by a sufficiently pronounced increase EF.

A similar trend was observed in patients with stented multiple CAs. After 6 months of treatment, the analysis of the structural and functional parameters of the myocardium according to the Echocardiogram data showed more pronounced positive dynamics in patients with the ivabradine-supplemented treatment complex. In a larger percentage value, the dimensions of the LV and LV and volume indicators - ESV and EDV of the left ventricle decreased.

After 12 months of treatment, in patients with OG and HP with multivessel lesions of the CA, the diameter of the LA decreased by 5.8% versus 2.1% ($p<0.05$), EDD LV by 3.7% versus 1.0% ($p<0.05$); LV ESD - by 4.1% versus 1.3%, ($p<0.05$); ESV LV by 9.5% versus 0.6% ($p<0.05$); PV by 6.3% versus 2.6% in MG and AH patients, respectively.

Optimizing the treatment of patients with intravascular coronary angioplasty with ivabradine after 6 months was confirmed by further observations regarding the intensity of changes in the size and volume of the heart according to Echocardiogram data.

After 12 months of treatment in MG patients, regardless of the number of stented coronary arteries, the studied hemodynamic parameters improved statistically and the pumping function of the myocardium increased ($p<0.05$). Greater dynamics were noted in patients with a stented single coronary artery, where the structural and functional parameters of the heart before the end of the study became identical to the same parameters of practically healthy individuals ($p<0,01$, $p<0,05$).

Comparing the trend of changes in the sizes of the LA and LV and their volumetric indicators between 6 and 12 months, it is clear that in patients who took BT drugs, the structural and functional parameters of the myocardium practically did not differ from the six-month indicators, and this did not depend on the number of stented coronary vessels. A statistically significant improvement in heart parameters was noted only in MG patients with stented CAs.

Thus, in patients after endovascular revascularization of the myocardium treated for 12 months with ivabradine and BT, there were significant changes in all parameters characterizing the size and function of the heart (both systolic and diastolic). In MG patients with stented one CA, compared to the moment of admission after 12 months of pharmacotherapy, the diameter of the LA decreased by 9.5% versus 2.3% in patients with AH, left ventricular EDD by 7.3% versus 2.1% in patients with AH; ESD of the left ventricle - by 5.7% against 1.6% in patients with AH; ESV of the left ventricle 21.6% against 3.5% in patients with AH; PV by 11.5% versus 2.9% in patients with AH, respectively (all $p<0.05$).

Analyzing the echocardiogram data in patients with stable angina pectoris with two or more stents installed, treated with ivabradine and BT drugs, after 12 months a decrease in the diameter of the left ventricle was established by 10.7% against 3.3% in CG, left ventricular EDD by 6.6% against 1.5% in CG, left ventricular ESD - by 8.1% against 1.7% in CG, left ventricular EDV 18.1% against 1.4% in CG, PV by 12.4% against 4.2% in CG, respectively ($p<0.05$).

After 12 months of therapy, ivabradine had a beneficial and reliable effect on the structural and functional parameters of the myocardium in patients with CIHD, which did not depend on the number of stented coronary arteries.

Natriuretic peptide is the main diagnostic biomarker of HF complicating IHD. The concentration of NT-proBNP after the use of pharmacotherapeutic complexes significantly decreased in all clinical groups of patients.

The content of NT-proBNP in healthy subjects was 178.7±17.62 fmol/ml. The amount of NT-proBNP in the serum of MG patients with single-vessel lesions of the CA before treatment was 690.67±15.80 fmol/ml, and 6 months after treatment - 398.00±9.60 fmol/ml, which is 42.4% less than before treatment ($p<0.05$). After 12 months, the amount of NT-proBNP was 281.33±8.55 fmol/ml, which was 59.3% less than before treatment ($p<0.05$). When two or more CAs were affected in MG patients, the content of NT-proBNP in blood serum 6 months after treatment significantly decreased by 40.2% (from 753.60±4.13 to 450.81±7.15 fmol/ml, $p<0.05$), and after 12 months the NT-proBNP indicator differed from the same level before treatment by 58.5% (up to 312.56±6.93 fmol/ml, $p<0.05$).

In CG patients with one CA affected before treatment, the level of NT-proBNP was 689.31±10.59 fmol/ml, after 6 months after treatment it significantly decreased by 41.2% and was 404.69±14.31 fmol/ml ($p<0.05$), after 12 months this indicator (395.31±11.61 fmol/ml) was not significantly different from the indicator after six months of treatment. In the same group of patients with lesions of two or more CA before treatment, the level of NT-proBNP was 752.72±15.76 fmol/ml, after 6 months it significantly decreased by 40.0% ($p<0.05$), and after 12 months of treatment was 454.89±13.48 fmol/ml, which did not significantly differ from the level of this prohormone in 6 months of treatment ($p>0.05$). When studying the relationship between cardiac volumetric parameters and NT-proBNP level depending on affected CA number (Fig.2, 3), there was observed a strong inverse correlation between LV EF and serum NT-proBNP level ($r=-0.77$, $p<0.05$ and $r=-0.86$, $p<0.05$).

Therefore, the use of ivabradine by patients with CIHD: angina pectoris III FC against the background of basic therapy within 12 months after the restoration of coronary circulation by stenting of coronary vessels optimizes the course of the disease, structural and functional indicators of the left ventricle and atrium, which generally stabilizes central and peripheral hemodynamics.

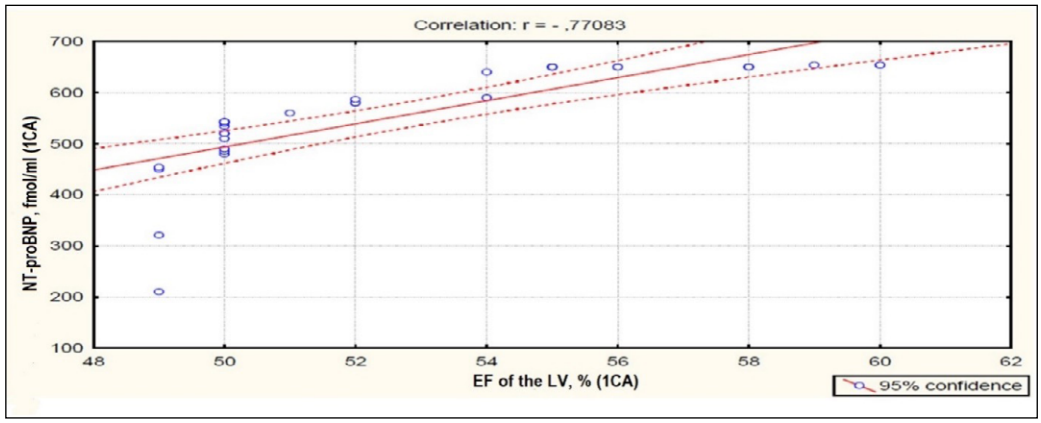

Fig.2. Correlation between EF LV and NT-proBNP in the patients with stable CIHD, namely FC III exertional angina, class IIA FC III HF with preserved and moderately reduced EF of the LV, single-vessel CAD.

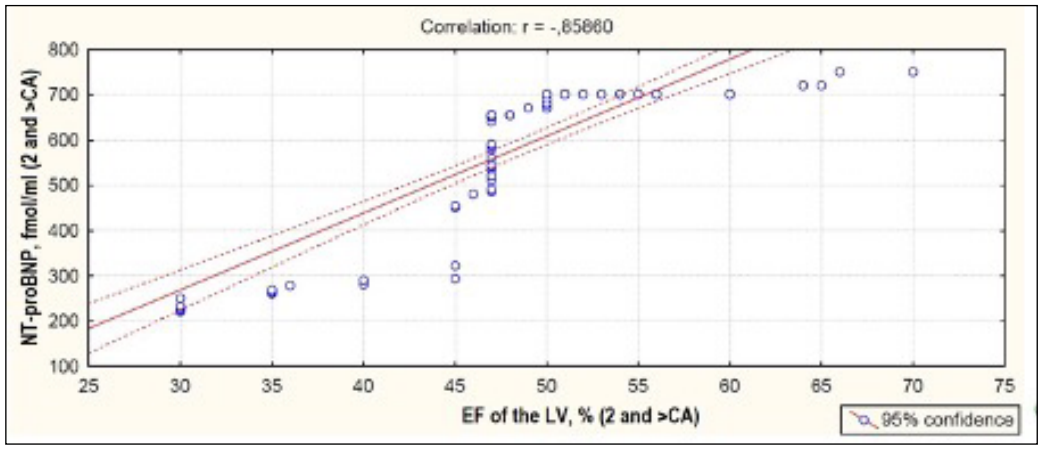

Fig.3. Correlation between EF LV and NT-proBNP in the patients with stable CIHD, namely FC III exertional angina, class IIA FC III HF with preserved and moderately reduced EF of the LV, multivessel CAD.

DISCUSSION

Our study describes the scheme of anti-ischemic therapy during 12 months of treatment for patients who underwent coronary artery stenting. The effectiveness of complete revascularization of the myocardium by implantation of DES-type stents has been demonstrated, regardless of the amount of atherosclerotic lesions of the coronary vessels. The results of our study are comparable to a meta-analysis [38], which included 7 studies and showed that DES implantation in the treatment of IHD, including lesions of the left main coronary artery, significantly reduces the risk of serious CV events and death from all causes and prevents the development and progression of HF. The TRYNON and DEFINITION trials demonstrated the high efficiency of coronary stenting using drug-eluting stents in patients with complex bifurcation lesions [39]. Thus, DES implantation is the optimal key to improving the results of treatment of patients with coronary artery disease, regardless of the number and location of coronary atherosclerosis lesions.

Undoubtedly, myocardial revascularization significantly improves the quality of life of patients with coronary heart disease, eliminating or significantly reducing the number of anginal attacks, but one should remember the pathogenetic mechanisms of the development of the pathology. Restorative treatment is a necessary part of the complex treatment of patients with coronary heart disease after endovascular revascularization of the myocardium.

Although multiple studies (SHIFT, CIBIS II, MERIT) have shown that reduction in heart rate is associated with improved clinical outcomes in patients with HF, it remains controversial whether the benefit of β-ABs is stronger by achieving target doses that help reduce heart rate [27]. Today, comorbidities of the pathology are of great importance, which is related to the optimal selection of pharmacotherapy of the disease. There are frequent clinical cases that make it impossible to use drugs from the β-AB group. These facts contribute to the intensive search for new drugs capable of regulating heart rhythm. According to the results of the HF-ACTION study, patients who received low-dose β-ABs for various reasons had worse outcomes for the endpoints of all-cause mortality and hospitalizations. There was a significant relationship between β-AB dose (the higher the better) and mortality from cardiac events [40].

Our results showed that ivabradine in combination with a minimum dose of β-AB maximally contributed to the remodeling of the myocardium, improved the prognosis regarding the development and progression of HF after coronary stenting. The hypothesis of the study was that ivabradine can significantly affect the reduction

of CV events in patients who underwent endovascular intervention on coronary vessels regardless of the number of stented CAs. The pharmacological effectiveness of ivabradine in these conditions is associated with its selective reduction of heart rate due to the effect on the If channels of the sinus node in the myocardium [26]. The effectiveness of ivabradine treatment in combination with BT drugs in patients with coronary artery disease and heart failure has been demonstrated in numerous studies (BEAUTIFUL, SHIFT, SIGNIFY), which prompted us to use this drug in the recovery period in patients after coronary stenting [27, 41].

For all patients with CIHS, regardless of the accompanying pathology and the number of affected CAs, complete myocardial revascularization with the installation of DES-type stents followed by pharmacotherapy with the inclusion of ivabradine in the treatment complex is an attractive treatment option, which is manifested by the stability of the course of the main pathology, prevents the development and progression of HF on long-term period.

CONCLUSIONS

1. Ivabradine in combination with BT drugs has a positive effect on central hemodynamic parameters: a decrease in LA and LV diameters in all patients, regardless of the number of affected CAs. During the 12 months of observation, a significant improvement in the structural and functional parameters of the heart was noted.
2. In patients with stented one CA, the structural and functional parameters of the heart after 12 months of treatment with ivabradine reached the values of practically healthy individuals from the control group. Regardless of the number of CAs affected by atherosclerosis, ivabradine promotes reverse remodeling of the left ventricle, regression of heart failure, which in turn will affect the minimization of the number of cardiac events.
3. When prescribing ivabradine, a decrease in the level of brain natriuretic peptide in blood serum was recorded 12 months after the start of endovascular and drug treatment by 59.3%, in contrast to the comparison group, where there is stability only up to 6 months of pharmacotherapy.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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RECEIVED: 10.11.2023
ACCEPTED: 15.03.2024